UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: May 18, 2011

SUBJECT: Sedaxane: Report of the Cancer Assessment Review Committee

PC Code: 129223
Decision No.: N/A
Petition No.: N/A
Risk Assessment Type: Cancer Assessment
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MRID No.: N/A

DP Barcode: N/A
Registration No.: N/A
Regulatory Action: N/A
Case No.: N/A

CAS No.: N/A
40 CFR: N/A

FROM: Jessica Kidwell, Executive Secretary
Cancer Assessment Review Committee
Health Effects Division (7509P)

THROUGH: Jess Rowland, Chair
Cancer Assessment Review Committee
Health Effects Division (7509P)

TO: William Irwin, Toxicologist
RAB V, Health Effects Division (7509P)

AND

Heather Garvie, RM 20
Fungicide Branch, Registration Division (7505P)

The Cancer Assessment Review Committee met on March 16, 2011 to evaluate the cancer classification of Sedaxane in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). Attached please find the final Cancer Assessment Document.

CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF

Sedaxane

***PC Code* 129223**

FINAL
May 18, 2011

CANCER ASSESSMENT REVIEW COMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS

DATA PRESENTATION: William A. Irwin
William Irwin, Toxicologist

DOCUMENT PREPARATION: Jessica Kidwell
Jessica Kidwell, Executive Secretary

COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the assessment unless otherwise noted.)

Gregory Akerman

Lori Brunsman, Statistician Lori Brunsman

Marion Copley Jess Rowland for MC

Kit Farwell

Ray Kent

Mary Manibusan

Nancy McCarroll Nancy McCarroll

Karlyn Middleton

Jess Rowland, Chair Jess Rowland

P.V. Shah P.V. Shah

NON-COMMITTEE MEMBERS IN ATTENDANCE: (Signature indicates concurrence with the pathology report)

John Pletcher, Consulting Pathologist

OTHER ATTENDEES: Jack Arthur, Jack Fowle, Heather Garvie, Abdallah Khasawinah, Alan Levy, Brenda May, Jessica Ryman, PMRA (Sathish Achuthan, Catherine Adcock, Carmen Cheung, Tina Singal, Stacey Stiege)

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EXECUTIVE SUMMARY

On March 16, 2011, the Cancer Assessment Review Committee (CARC) of the Health Effects Division (HED) of the Office of Pesticide Programs (OPP) met to evaluate the carcinogenic potential of Sedaxane.

William Irwin of Risk Assessment Branch V presented the chronic toxicity/carcinogenicity study in Crl:WI(Han)(Han Wistar) rats and the carcinogenicity study in Crl:CD-1(ICR) mice. In a combined chronic toxicity/carcinogenicity study, 52 Crl:WI(Han)(Han Wistar) rats/sex/dose were exposed to Sedaxane (95.3% a.i.) for up to 2 years in the diet at concentrations of 0, 200, 1200, or 3600 ppm (equivalent to 0/0, 11/14, 67/86, and 218/261 mg/kg bw/day in males/females, respectively). Additionally, 12 rats/sex/dose were treated similarly for up to 1 year and then sacrificed. In a carcinogenicity study, Sedaxane (95.3% a.i) was administered in the diet to Crl:CD-1(ICR) mice (50/sex/dose) for up to 80 weeks at doses of 0, 200, 1250, or 7000 ppm (equivalent to 0/0, 25/29, 157/185, and 900/1001 mg/kg bw/day in males/females). Mutagenicity data and structure activity relationship were also discussed.

The CARC considered the following for a weight-of-evidence determination of the carcinogenic potential of Sedaxane.

Carcinogenicity

Rat

• *Liver Tumors:* In male Wistar rats, liver tumors were limited to adenomas; no carcinomas were seen. Although a statistically significant trend was seen for liver adenomas at $p<0.05$, there were no significant pair-wise comparisons of the dosed groups with the controls. The concurrent control incidence (2%) was within the laboratory historical control range (0-3%); however, the incidence of liver adenomas at the high dose (10%) exceeded the historical control range. No pre-cursor lesions of the liver were seen in males at this dose. **The CARC considered the liver adenomas to be weak evidence of a treatment-related effect only at the high dose in male rats.**

• *Thyroid Tumors:* Male Wistar rats had statistically significant trends for thyroid follicular cell adenomas and thyroid follicular cell combined adenomas and/or carcinomas, both at $p < 0.05$. There were no significant pair-wise comparisons of the dosed groups with the controls. The concurrent control incidences of adenomas, carcinomas and combined were within the laboratory historical control ranges; however, the combined incidences exceeded the laboratory control ranges. The thyroid tumors were supported by the presence of precursor lesions in the thyroid (increased follicular cell hyperplasia). **The CARC considered the thyroid tumors to be weak evidence of a treatment-related effect only at the high dose in male rats.**

• *Uterine Tumors:* The incidences of combined uterine tumors (adenomas and adenocarcinomas)

were significantly increased at all dose levels. No precursor lesions were seen at any dose level. Female Wistar rats had statistically significant trends, and significant pair-wise comparisons of the 3600 ppm dose group with the controls, for uterine adenocarcinomas and combined adenomas and/or adenocarcinomas, all at $p < 0.01$. There was a statistically significant pair-wise comparison of the 1200 ppm dose group with the controls for uterine combined adenomas and/or adenocarcinomas at $p < 0.05$. There was also a statistically significant pair-wise comparison of the 200 ppm dose group with the controls for uterine adenocarcinomas and combined adenomas and/or adenocarcinomas, both at $p < 0.05$. The CARC observed that uterine tumors were present in structurally related chemicals. **The CARC considered the uterine tumors to be treatment-related in female rats.**

• *Adequacy of Dosing:* In both males and female rats, the high dose of 3600 ppm was considered to be adequate, but not excessive, to assess the carcinogenicity of sedaxane. Significant ($p<0.01$) decreases in absolute body weights were seen in males (17.8%) and females (33.1%). Body weight gains were significantly ($p<0.01$) decreased in males (23.5%) and females (49.1%). Although the observed body weight/body weight gains changes exceeded the conventional 10% criteria employed for assessment of body weight changes in carcinogenicity studies, the CARC did not consider the high dose (3600 ppm) to be excessive in either sex since there was no evidence of adverse toxicity (e.g., mortality, clinical signs at this dose). In addition, significant increases in liver weights were seen in males (absolute and relative) and females (relative), as well as treatment-related non-neoplastic lesions in the liver and thyroid glands in both sexes and in the kidneys and vagina in the females. Survival in males and females was not affected at the high dose.

Mouse

• *Liver Tumors:* Male CD-1 mice had statistically significant trends, and significant pair-wise comparisons of the 7000 ppm dose group with the controls, for hepatocellular adenomas and combined adenomas and/or carcinomas, all at $p < 0.05$. There was also a statistically significant trend in hepatocellular carcinomas at $p < 0.05$. The incidences of liver adenomas, carcinomas and combined exceeded the laboratory historical control ranges. There were no precursor lesions of the liver at this dose. **The CARC considered the liver tumors to be treatment-related only at the high dose in male mice.**

• *Adequacy of Dosing:* The high dose of 7000 ppm was considered to be adequate, but not excessive, in both male and female mice to assess the carcinogenicity of sedaxane. The highest dose tested was the limit dose.

Mutagenicity: There is no concern for mutagenicity.

Structure Activity Relationship: Sedaxane is a member of the pyrazole-carboxamide class of succinate dehydrogenase inhibitor fungicides. Other similar analogs include bixafen and isopyrazam. Isopyrazam was classified as "Likely to be Carcinogenic to Humans" based on the presence of thyroid follicular cell tumors in male rats, and liver and uterine tumors in female rats.

Classification and Quantification of Carcinogenic Potential

In accordance with the EPA's *Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC classified Sedaxane as **"Likely to be Carcinogenic to Humans".** This classification is based on the presence of liver and thyroid tumors in male rats, uterine tumors in female rats and liver tumors in male mice. Uterine tumors were also seen in a chemical structurally related to Sedaxane. There is no mutagenic concern for Sedaxane.

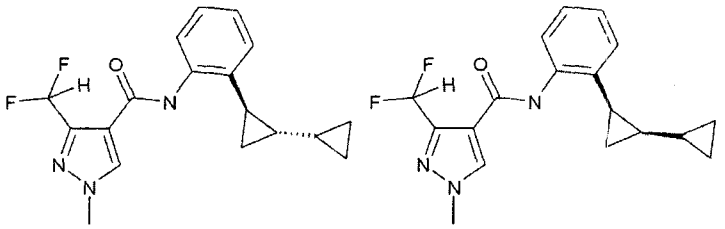
A linear low-dose extrapolation model (Q_1*) will be used for quantification of cancer risk to humans.

I. INTRODUCTION

On March 16, 2011, the Cancer Assessment Review Committee of the Health Effects Division of the Office of Pesticide Programs will meet to evaluate the carcinogenic potential of Sedaxane.

II. BACKGROUND INFORMATION

Sedaxane is a new chemical with a petition for the establishment of use as a seed treatment on barley, canola, oat, rye, soybean, triticale, and wheat. The PC Code is 129223 and the CAS number is 874967-67-6. This CARC is part of a global review. Canada is the primary reviewer for the toxicology data, and the USA is the secondary reviewer.



Trans isomer (SYN508210) Cis isomer (SYN508211)

Structure of Sedaxane Isomers

Sedaxane (SYN524464) is a pyrazole carboxamide which is used as a broad spectrum fungicide belonging to the class of ortho-substituted phenyl amides with similar structure to isopyrazam and bixafen. As their fungicidal MOA, this class of chemicals inhibits succinate dehydrogenase (Complex II) which is a functional part of the citric acid cycle and the mitochondrial electron transport chain. A special 28-day study in the rat revealed with EM images that sedaxane caused fragmented mitochondria and decreased glycogen content in the liver, consistent with mitochondrial inhibition in rodents as well.

Sedaxane has two diasterioisomers (epimers): trans and cis isomers, both are biologically active. The mammalian toxicity and ADME studies were typically conducted with a test material containing 95.3 % w/w, comprised of 83.0% *trans* isomer and 12.3% *cis* isomer. The minimum sedaxane purity is 95.0%. For both isomers excretion was fairly rapid (almost complete by 72 hours post dosing) with a significant proportion of the administered radioactivity being excreted by 24 hours post dosing. The absorbed radioactivity was rapidly distributed throughout the tissues and rapidly cleared without accumulation of radio-labeled SYN524464 in the tissues. Sedaxane is of low acute toxicity by the oral, dermal, and inhalation routes. It is not irritating to the skin, but minimally irritating to the eyes. Sedaxane is not a skin sensitizer. Sedaxane was negative for mutagenicity and clastogenicity in a battery of in vitro and in vivo studies.
The primary target organ is the liver and most studies consistently demonstrate that in several species. The principle effect is increased organ weight and hepatocyte hypertrophy. The liver toxicity is generally accompanied by body weight and food consumption reductions.

III. EVALUATION OF CARCINOGENICITY STUDIES

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

Reference: SYN524464 - 104 Week Rat Dietary Carcinogenicity Study with Combined 52 Week Toxicity Study. Charles River, Tranent, Edinburgh, EH33 2NE, UK. Laboratory Report No. 30196 issue date: 10 February 2010. Unpublished. (Syngenta File No. SYN524464_11306). PMRA #1897899. MRID #47473386.

A. Experimental Design

In a chronic toxicity study, SYN524464 (95.3% a.i.) was administered to 52 Crl:WI(Han) (Han Wistar) rats/sex/dose in diet at dose levels of 0, 200, 1200 or 3600 ppm (0, 11, 67 or 218 mg/kg bw/day in males and 0, 14, 86 or 261 mg/kg bw/day in females) for at least 104 consecutive weeks. In addition, a toxicity study comprising 12 Han Wistar rats/sex/dose were included and dosed in an identical fashion for a period of 52 consecutive weeks.

B. Discussion of Tumor Data

Survival Analysis

There were no survival disparities among the dose groups for male rats (Table 1). In female rats mortality at the mid- and high-dose groups was comparable to the controls, however, those at the low dose (200 ppm) had a higher mortality rate (significant pair-wise comparison at $p < 0.05$) when compared to controls (Table 2; L. Brunsman, TXR #0055689).

Table 1. Sedaxane – Crl:WI(Han)(Han Wistar) Rat Study (MRID 47473386)

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose (ppm)	1-26	27-53	53[i]	54-78	79-105[f]	Total
0	0/64	0/64	12/64	1/52	8/51	9/52 (17%)
200	1/64	0/63	12/63	2/51	9/49	12/52 (23%)
1200	0/64	0/64	12/64	3/52	6/49	9/52 (17%)
3600	0/64	0/64	12/64	2/52	6/50	8/52 (15%)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.
[i]Interim sacrifice at week 53;
[f]Final sacrifice at week 105
( )Percent

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control (the p values on the control groups are the trends).
Significance of pair-wise comparison with control group (dose 0) denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Table 2. Sedaxane – Crl:WI(Han)(Han Wistar) Rat Study (MRID 47473386)

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks					
Dose (ppm)	1-26	27-53	53[i]	54-78	79-105[f]	Total
0	1/64	0/63	12/63	0/51	7/51	8/52 (15%)
200	0/63[a]	1/63	11/62	4/51	12/47	17/52 (33%)*
1200	0/63[a]	0/63	11/63	2/52	12/50	14/52 (27%)
3600	1/64	1/62[b]	10/61	1/51	6/50	9/53 (17%)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.
[i]Interim sacrifice at week 53.
[f]Final sacrifice at week 105.
( )Percent.
[a]One accidental death at week 24 in each of the 200 and 1200 ppm dose groups.
[b]One accidental death at week 33, dose 3600 ppm.

Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control (the p values on the control groups are the trends).
Significance of pair-wise comparison with control (dose 0) denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Tumor Analyses

Tumors were observed in the liver and thyroid glands of male rats and in the uterus of female rats (L. Brunsman, TXR #0055689).

a) Liver tumors: No liver tumors were seen in female rats. As shown in Table 3 below, among males, liver tumors were limited to adenomas; no carcinomas were seen. Although a significant trend was seen for adenomas at $p<0.05$, there were no significant pair-wise comparisons of the dosed groups with the controls. The concurrent control incidence was comparable to the historical control mean (1.2%) and range (0-3%).

Table 3. Sedaxane – Crl:WI(Han)(Han Wistar) Rat Study (MRID 47473386)

Male Liver Tumor Rates[+]
and Fisher's Exact Test and Exact Trend Test Results

	Dose (ppm)			
	0	200	1200	3600
Adenomas# (%)	1/52 (2%)	1[a]/51 (2%)	1/52 (2%)	5/52 (10%)
p =	0.01656*	0.74757	0.75243	0.10248

+Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.
#No carcinomas were observed.
[a]First adenoma observed at week 89, dose 200 ppm.

Note: Significance of trend denoted at control (the p values on the control groups are the trends).
Significance of pair-wise comparison with control (dose 0) denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Laboratory Control Adenomas: Range is 0-3%, Mean is 1.2%, SD is 1.3% (N=5 Studies)
Laboratory Control Carcinomas: Range is 0-2%, Mean is 0.6%, SD is 0.9% (N=5 Studies)
Laboratory Control Total Tumors: Range is 0-5%, Mean is 1.8%, SD is 2.0% (N=5 Studies)

b) Thyroid tumors: No thyroid tumors were seen female rats. As shown in Table 4 below, among male rats, statistically significant trends were seen for follicular cell adenomas and combined adenomas and/or carcinomas, both at $p<0.05$. There were no significant pair-wise comparisons of the dosed groups with the controls. The concurrent control incidence of adenomas was within the historical control mean (6.8%) and range (2-11%). For carcinomas, there was no significant trend or pair-wise comparisons of the dosed groups with the controls. The combined tumor increase was driven mainly by the adenomas (i.e., no malignant component). The concurrent control incidences of the combined tumors were within the historical control mean (6%) and range (2-25%).

Table 4. Sedaxane – Crl:WI(Han)(Han Wistar) Rat Study (MRID 47473386)

Male Thyroid Follicular Cell Tumor Rates[+]
and Fisher's Exact Test and Exact Trend Test Results

	Dose (ppm)			
	0	200	1200	3600
Adenomas (%) p =	3[a]/52 (6%) 0.0299*	3/50 (6%) 0.6421	4/52 (8%) 0.5000	8/52 (15%) 0.1004
Carcinomas (%) p =	0/52 (0%) 0.2056	0/50 (0%) 1.0000	2[b]/52 (4%) 0.2476	1/52 (2%) 0.5000
Combined (%) p =	3/52 (6%) 0.0182*	3/50 (6%) 0.6421	6/52 (12%) 0.2439	9/52 (17%) 0.0611

+Number of tumor bearing animals/Number of animals examined, excluding those that died or were sacrificed before week 54.
[a]First adenoma observed at week 87, dose 0 ppm.
[b]First carcinoma observed at week 87, dose 1200 ppm.

Note: Significance of trend denoted at control (the p values on the control groups are the trends).
Significance of pair-wise comparison with control (dose 0) denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Laboratory Control Adenomas: Range is 2-11%, Mean is 6.8%, SD is 3.4% (N=5 Studies)
Laboratory Control Carcinomas: Range is 0-6%, Mean is 1.8%, SD is 2.7% (N=5 Studies)
Laboratory Control Total Tumors: Range is 2-15%, Mean is 8.0%, SD is 4.7% (N=5 Studies)

c) Uterine tumors: As shown in Table 5 below, no statistically significant increases were seen for uterine adenomas. Female rats had a statistically significant trend ($p<0.01$), and significant pair-wise comparisons of the 200 ppm ($p<0.05$) and 3600 ppm dose groups ($p<0.01$) with the controls, for uterine adenocarcinomas. There was a statistically significant trend ($p<0.01$) and significant pair-wise comparisons of the 200 ppm ($p<0.05$), 1200 ppm ($p<0.05$) and 3600 ppm ($p<0.01$) dose groups with the controls for combined tumors. It should be noted that while no adenocarcinomas were seen in the concurrent controls in this study, the historical control data from 5 studies shows a mean of 10.4% (with a range was 0-19%) for this tumor type. The incidences of the combined tumors (adenomas+ adenocarcinomas) were significantly increased at all dose levels. No combined tumors were seen in the concurrent controls, whereas the historical control data for the combined tumors ranged from 2-22% with a mean of 12.6%).

Table 5. Sedaxane – Crl:WI(Han)(Han Wistar) Rat Study (MRID 47473386)

Female Uterine Tumor Rates[+]
and Peto's Prevalence Test Results

	Dose (ppm)			
	0	200	1200	3600
Adenomas (%) p =	0/44 (0%) 0.52989	0/35 (0%) -	1[a]/38 (3%) 0.14095	0/44 (0%) -
Adenocarcinomas (%) p =	0/50 (0%) 0.00033**	3/43 (7%) 0.02457*	2/44 (5%) 0.08172	9[b]/49 (18%) 0.00080**
Combined (%) p =	0/50 (0%) 0.00053**	3/43 (7%) 0.02457*	3/44 (7%) 0.03866*	9/49 (18%) 0.00080**

+Number of tumor bearing animals/Number of animals examined, excluding those that died before observation of the first tumor.

[a]First adenoma observed at final sacrifice, dose 1200 ppm.

[b]First carcinoma observed at week 89, dose 3600 ppm.

Note: Significance of trend denoted at control (the p values on the control groups are the trends).
Significance of pair-wise comparison with control (dose 0) denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Laboratory Control Adenoma: Range is 0-4%, Mean is 2.8%, SD is 1.8% (N=5 Studies)
Laboratory Control Adeno. Carc.: Range is 0-19%, Mean is 10.4%, SD is 7.0% (N=5 Studies)
Laboratory Control Total Tumors: Range is 2-22%, Mean is 12.6%, SD is 7.2% (N=5 Studies)

C. Non-Neoplastic Lesions

a. Non-neoplastic:

The non-neoplastic lesions observed in this study are presented in Tables 6 and 7 and liver weights are presented in Table 8.

Liver: At the interim sacrifice (52 weeks) significant increases in hepatocyte pigment and centrilobular hepatocyte hypertrophy was seen in males and females at the high dose (Table 6). At the terminal sacrifice (104 weeks), eosinophillic cell foci were significantly increased at the high dose in males and in females at all doses in females. These incidences, however, were within the historical control range for the males (16-86%) and females (7-32%). Centrilobular hepatocyte hypertrophy was significantly ($p<0.01$) increased at the mid and high ($p<0.001$) dose groups in males and at the high dose ($p<0.001$) in females (Table 7).

D. Adequacy of the Dosing for Assessment of Carcinogenicity

For this study, the high dose (3600 ppm; 218 mg/kg/day) was selected based on the results of the range-finding (28 days) and subchronic (90 days) studies. In the subchronic study, the LOAEL was 168/186 mg/kg/day in males and females, respectively, based on adverse effects on body weight, body weight gain and changes in liver, thyroid and kidney weights.

The high dose in the combined carcinogenicity/chronic toxicity study was considered to be adequate in both sexes based on the following considerations: significant ($p<0.01$) decreases in absolute body weights were seen in males (17.8%) and females (33.1%); body weight gains were significantly ($p<0.01$) decreased in males (23.5%) and females (49.1%); significant ($p<0.1$) increases in liver weights were seen in males (absolute and relative) and females (relative); treatment-related non-neoplastic lesions were seen in the liver and thyroid glands in both sexes and in the kidneys and vagina in the females; and neoplastic lesions manifested as hepatocellular adenomas and thyroid follicular cell tumors in males and adenocarcinomas in the females.

Figure 1: Body weight data in Male Rats Fed Diets Containing Sedaxane for 2-years

Two Year Rat Study:
Male Body Weights vs. Control

3600 ppm: 52 wks -13.9%**
104 wks -17.8%**
BW gain: 52 wks -19.1%**
104 wks -23.5%**

1200 ppm: no effect

200 ppm: 52 wks +3.2%
104 wks +7.7%*

Statistically significant at $p<0.05$ (*)
or $p<0.01$ (**)

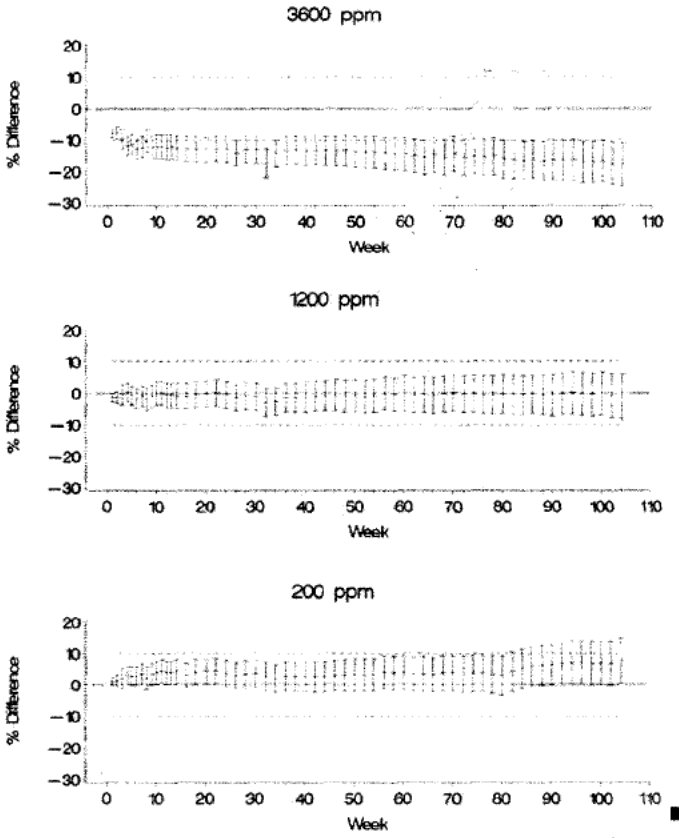


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Figure 2: Body weight data in Female Rats Fed Diets Containing Sedaxane for 2-years

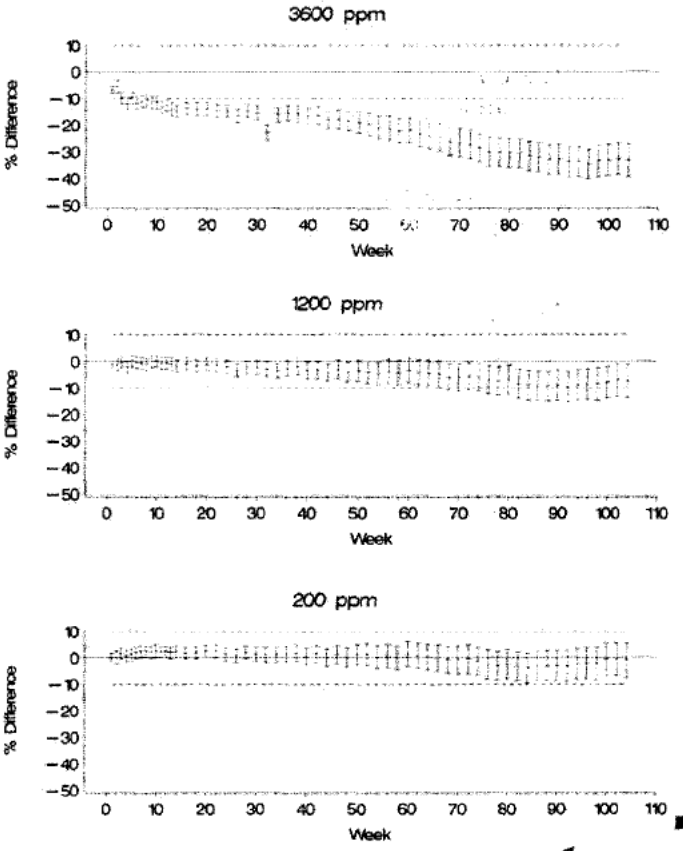
Two Year Rat Study:
Female Body Weights vs. Control

3600 ppm: 52 wks -19.7%**
104 wks -33.1%**
BW gain: 52 wks -34.7%**
104 wks -49.1%**

1200 ppm: 52 wks -4.1%
104 wks -7.5%*
BW gain: 52 wks -8.1%*
104 wks -11.4%**

200 ppm: no effect

Statistically significant at p<0.05 (*)
or p<0.01 (**)



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10 [redacted]

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Table 6. Select Microscopic Changes in the Rat (52 weeks) [a]

mg/kg bw/d	0 n =12	11 n = 12	67 n = 12	218 n = 12
Males				
Liver				
Basophilic cell focus, tigroid	1	1	0	0
Clear cell focus	11	6	9	4**
Hepatocyte hypertrophy, centrilobular	0	0	0	11***
Hepatocyte pigment	0	0	0	7**
Thyroid Gland				
Follicular cell hypertrophy	0	0	5*+	4+
mg/kg bw/d	**0** **n = 12**	**14** **n = 12**	**86** **n = 12**	**261** **n = 12**
Females				
Liver				
Basophilic cell focus, tigroid	5	1	0*	0*
Clear cell focus	1	0	1	1
Hepatocyte hypertrophy, centrilobular	0	0	0	12***
Hepatocyte pigment	1	1	1	7*
Thyroid Gland				
Follicular cell hypertrophy	0	0	2	3

[a] Data extracted from pages 475-481 of the study report.

*p<0.05, **p<0.01; ***p<0.001, pair-wise Fisher's Exact Test

+p<0.05, Mann-Whitney U-test. Other Mann-Whitney results for the indicated statistical results were similar to Fisher's test results.

Table 7. Select Microscopic Changes in the Rat (104 weeks)[a]

mg/kg bw/d	0	11	67	218
Males				
Kidney, n	52	52	52	52
Chronic progressive nephropathy	33	36	37	37
Pelvic mineralization	14	9	5*	5*
Inflammation/inflammatory cell infiltration	7	3	5	8
Transitional cell hyperplasia	11	15	10	5
Liver, n	52	52	52	52
Eosinophilic cell focus (% n)	8 (15.4)	7 (13.5)	15 (28.8)	25*** (48.1)
Historical Range at Laboratory of eosinphilic cell focus	16-86%			
Basophilic cell focus, homogenous	2	0	1	0
Basophilic cell focus, tigroid	4	7	6	5
Clear cell focus	33	39	37	19*
Hepatocyte hypertrophy, centrilobular	0	0	8**	16***
Hepatocyte pigment	0	1	0	1
Mammary gland, n	43	43	45	41
Lobular hyperplasia	7	1	1*	4
Thymus, n	52	50	48	49
Hyperplasia, epithelial tubular	3	1	5	5
Thyroid, n	52	52	52	52
Desquamation, epithelial follicular	7	8	11	16
Basophilia, colloid	7	9	12	16+
Diffuse C-cell hyperplasia	27	27	24	10***
Focal follicular cell hyperplasia	7	8	8	16+
mg/kg bw/d	0	14	86	261
Females				
Kidney, n	52	52	52	52
Chronic progressive nephropathy	24	22	20	9**
Pelvic mineralization	30	36	33	9***
Inflammation/inflammatory cell infiltration	8	9	10	19*
Transitional cell hyperplasia	29	37	37	17*
Liver, n	52	52	52	52
Eosinophilic cell focus (% n)	2 (3.8)	10* (19.2)	12** (23.1)	14** (26.9)

mg/kg bw/d	0	11	67	218
Historical Range at Laboratory of eosinphilic cell focus	7-32%			
Basophilic cell focus, tigroid	36	35	43	31
Clear cell focus	12	16	14	12
Hepatocyte hypertrophy, centrilobular	0	0	1	38***
Hepatocyte pigment	2	3	1	15***
Mammary gland, n	52	50	51	52
Lobular hyperplasia	34	34	32	21*
Thymus, n	50	52	50	51
Hyperplasia, epithelial tubular	18	17	18	31*
Thyroid, n	52	52	52	52
Desquamation, epithelial follicular	2	5	9*	14**
Basophilia, colloid	3	6	11*	17***
Diffuse C-cell hyperplasia	29	31	27	5***
Focal follicular cell hyperplasia	0	4+	0	4+
Vagina, n	51	52	52	52
Mucification	15	22	16	3**

[a] Data extracted from pges 486-517 of the study report.
*p<0.05, **p<0.01; ***p<0.001, pairwise Fisher's Exact Test
+p<0.05, Mann-Whitney U-test. Mann-Whitney U-test results for the other indicated statistical results were similar to Fisher's test results. Desquamation , epithelial follicular was not evaluated by the Mann-Whitney U-test.

Table 8. Select Average Organ Weights (g) in the Rat (% Change) (104 weeks) [a]

mg/kg bw/d	0 n = 43	11 n = 40	67 n = 43	218 n = 44
		Males		
Final BW	611 ± 99	654 ± 101 (+7)	588 ± 79	504 ± 75** (-18)
Absolute Liver	18.57 ± 2.79	19.40 ± 2.69	20.21 ± 3.00* (+9)	22.52 ± 3.49** (+21)
Adjusted Liver	18.10 ± 0.37	18.06 ± 0.41	20.21 ± 0.37** (+12)	24.20 ± 0.41** (+34)
mg/kg bw/d	**0** **n = 44**	**14** **n = 35**	**86** **n = 37**	**261** **n = 44**
		Females		
Final BW	388 ± 59	389 ± 56	363 ± 56 (-6)	266 ± 28** (-31)
Absolute Liver	12.72 ± 2.06	13.24 ± 2.80	13.07 ± 2.29	12.17 ± 1.54
Adjusted Liver	11.56 ± 0.26	12.05 ± 0.28	12.65 ± 0.26** (+9)	14.64 ± 0.31** (+27)

[a] Data extracted from pages 170-174 of the study report.
* Statistically significant difference from control group mean, p<0.05 (Dunnett's test, 2-sided)
** Statistically significant difference from control group mean, p<0.01 (Dunnett's test, 2-sided)

2. Carcinogenicity Study in Mice

Reference: SYN524464 – 80 Week Mouse Dietary Carcinogenicity Study. Charles River, Tranent, Edinburgh EH33 2NE, UK. Laboratory Report No. 30194 issue date. 28 January 2010. Unpublished. (Syngenta File No. SYN524464_11261). PMRA #1897905. MRID #47473388.

A. Experimental Design

In a carcinogenicity study, SYN524464 (Sedaxane) (95.3% a.i.) was administered in diet to groups of CD-1 mice (50/sex/group) at dose levels of 0, 200, 1250 or 7000 ppm (0, 25, 157, and 900 mg SYN524464/kg/day for males and 0, 29, 185, and 1001 mg SYN524464/kg/day for females) for 80 weeks.

B. Discussion of Tumor Data

Survival Analysis

There were no survival disparities among the dose groups for male mice (Table 9; L. Brunsman, TXR #0055689).

Table 9. Sedaxane – Crl:CD-1(ICR) Mouse Study (MRID 47473388)

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

	Weeks			
Dose (ppm)	1-26	27-52	53-82[f]	Total
0	1/50	1/49	16/48	18/50 (36%)
200	1/50	6/49	9/43	16/50 (32%)
1250	1/50	5/49	10/44	16/50 (32%)
7000	2/50	1/48	12/47	15/50 (30%)

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.
[f]Final sacrifice at week 82.
( )Percent.
Note: Time intervals were selected for display purposes only.
Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Tumor Analysis

Male mice had statistically significant trends, and significant pair-wise comparisons of the 7000 ppm dose group with the controls, for hepatocellular adenomas and combined adenomas and/or carcinomas, all at $p < 0.05$. There was also a statistically significant trend only in hepatocellular carcinomas at $p < 0.05$. The statistical analyses of the tumors in the male mice were based upon Fisher's Exact Test for pair-wise comparisons and the Exact Test for trend (Table 10; L. Brunsman, TXR #0055689). No liver tumors were seen female mice.

The concurrent control incidences of hepatocellular adenomas (15%) and the combined tumors (adenomas+carcinomas) (19%) were comparable to the historical control mean (20%) and range (10-28%) for adenomas, but slightly lower than the mean (23.3%) and range (22-28%) range for the combined tumors.

Table 10. Sedaxane – Crl:CD-1(ICR) Mouse Study (MRID 47473388)

Male Liver Tumor Rates[+]
and Fisher's Exact Test and Exact Trend Test Results
Dose (ppm)

	0	200	1250	7000
Adenomas (%)	7/48 (15%)	9[a]/45 (20%)	10/45 (22%)	15/48 (31%)
p =	0.03257*	0.33833	0.24710	0.04389*
Carcinomas (%)	5/48 (10%)	5/45 (11%)	3/45 (7%)	10[b]/48 (21%)
p =	0.03355*	0.58799	0.84447	0.13028
Combined (%)	9[c]/48 (19%)	13[d]/45 (29%)	12[d]/45 (27%)	19[e]/48 (40%)
p =	0.02295*	0.18263	0.25329	0.02113*

+Number of tumor bearing animals/Number of animals examined, excluding those that died before week 49.

[a]First adenoma observed at week 49, dose 200 ppm.
[b]First carcinoma observed at week 67, dose 7000 ppm.
[c]Three animals in the control group had both an adenoma and a carcinoma.
[d]One animal in each of the 200 and 1250 ppm dose groups had both an adenoma and a carcinoma.
[e]Six animals in the 7000 ppm dose group had both an adenoma and a carcinoma.

Note: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$.

Laboratory Control Adenomas: Range is 10-28%, Mean is 20.0%, SD is 9.2% (N=3 Studies)
Laboratory Control Carcinomas: Range is 6-10%, Mean is 7.3%, SD is 2.3% (N=3 Studies)
Laboratory Control Total Tumors: Range is 22-28%, Mean is 23.3%, SD is 4.2% (N=3 Studies)

C. Non-Neoplastic Lesions

All non-neoplastic histology findings were considered background findings associated with the age and strain of mice, for this kind of study conducted at the testing laboratory (Charles River, Edinburgh, UK).

D. Adequacy of Dosing for Assessment of Carcinogenicity

The highest dose tested was the Limit Dose (7000 ppm; approximately 1000 mg/kg/day) and was considered to be adequate, but not excessive, for both sexes. There were no adverse effects on survival, body weight (minimal loss of 5% in males and 8% in females), clinical signs, or adverse non-neoplastic lesions. In males, liver tumors occurred at the limit dose. In females, sedaxane showed no evidence of carcinogenicity even when exposed at the limit dose.

Table 11. Selected Organ Weight (g) and Group Mean Values with Standard Deviation (absolute and adjusted)[a]

	Dietary Concentration of SYN524464 (mg/kg/day)			
Males				
Organ	**0 (n = 32)**	**25 (n = 34)**	**157 (n = 33)**	**900 (n = 34)**
Final BW	60.8 (9)	58.8 (8.5)	57.9 (8.1)	57.6 (8)
Absolute – Liver	3.20 (1.34)	3.13 (0.88)	3.09 (0.74)	3.44 (1.05)
Adjusted – Liver	3.04 (0.798)	3.13 (0.812) (n = 32)	3.15 (0.804) (n = 32)	3.53* (0.812) (n = 32) (↑16%)
Absolute – Adrenal	0.0057 (0.0029) (n = 31)	0.0058 (0.0021)	0.0051 (0.0027) (n = 32)	0.0061 (0.0026) (n = 32)
Adjusted – Adrenal	0.0056 (0.0028) (n = 31)	0.0057 (0.0023)	0.0052 (0.0029) (n = 32)	0.0061 (0.0029) (n = 32)
Females				
Organ	**0 (n = 34)**	**29 (n = 38)**	**185 (n = 41)**	**1001 (n = 38)**
Final BW	47.9 (10)	47.3 (10.7)	48 (10.3)	44.8 (8.9)
Absolute – Liver	2.15 (1.29)	1.98 (0.64)	2.02 (0.50)	2.11 (0.45)
Adjusted – Liver	2.13 (0.696)	1.97 (0.739)	1.99 (0.704)	2.17 (0.739)
Absolute – Adrenal	0.0084 (0.0021)	0.0095 (0.0026) (n = 37)	0.0101* (0.0032) (↑20%)	0.0100 (0.0029)
Adjusted – Adrenal	0.0084 (0.0029)	0.0095 (0.00304) (n = 37)	0.0101* (0.00256) (↑20%)	0.0100 (0.0030)

[a] Data obtained from pages 105-108 in the study report

* Significantly different from control, $p<0.05$ by Dunnett's test

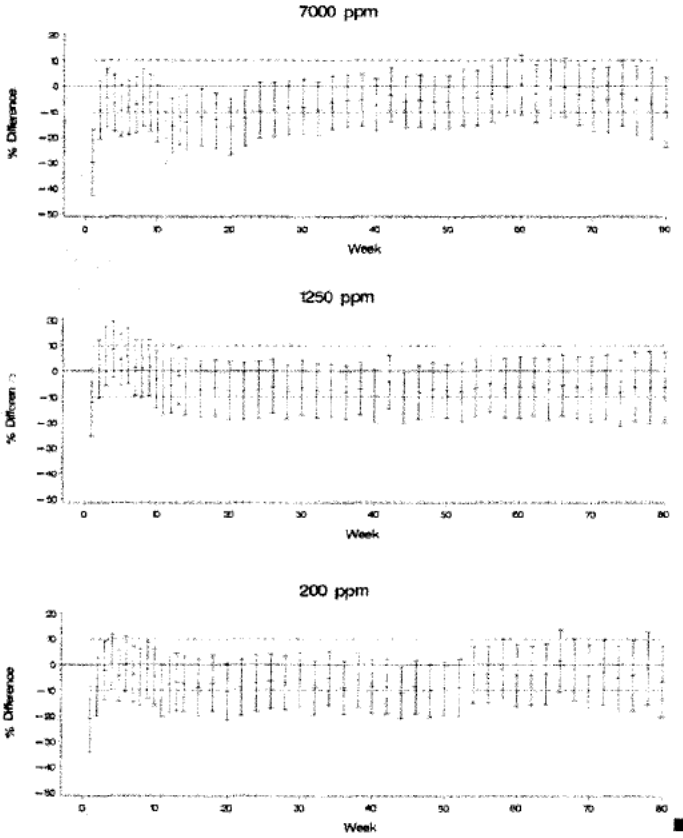
18-Mo. Mouse Study:

Male Body Wt Gain vs. Control

7000 ppm: only occasional statistical significance (0-5% decrease in BW)

1250 ppm: no effect

200 ppm: no effect



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27 [redacted]

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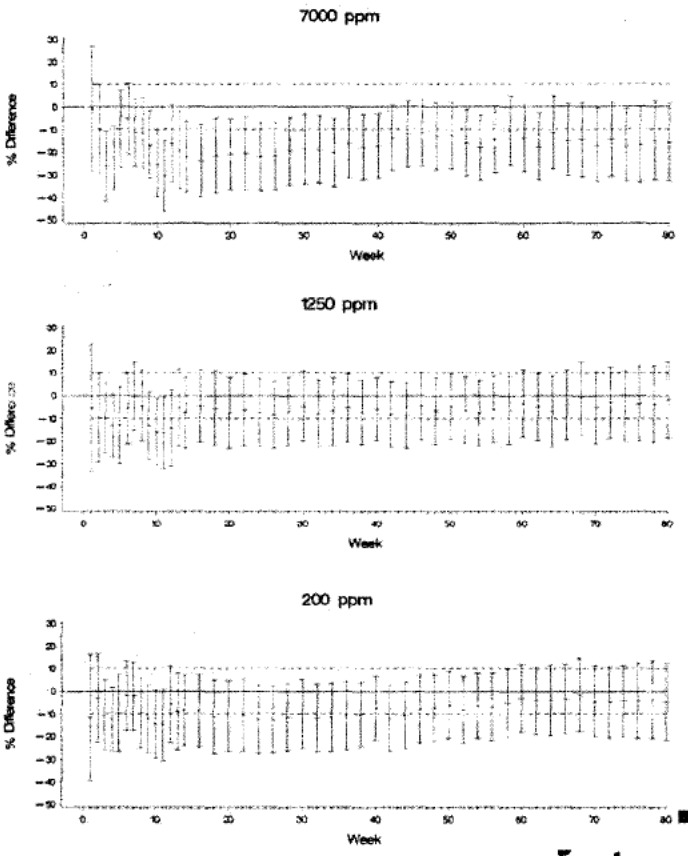
18-Mo. Mouse Study:
Female Body Wt Gain
vs. Control

7000 ppm: statistically significant decrease; not excessive (max 8% decrease in BW)

1250 ppm: no effect

200 ppm: no effect



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IV. TOXICOLOGY

1. Metabolism

Sedaxane Excretion and Tissue Distribution in the Rat Following Single Oral Administration of 1 mg or 80 mg [Pyrazole-5-^{14}C]-SYN524464/kg (MRID #47473359) Recoveries of radioactivity ranged between 96.3-104.9% AD, with no significant differences in tissue distribution or excretion between the dose levels. The primary route of excretion of [pyrazole-^{14}C]-SYN524464 was via the feces in both sexes, with urinary excretion slightly higher in females. The absorbed radioactivity was rapidly distributed throughout the tissues and rapidly cleared without accumulation of radio-labeled SYN524464 in the tissues.

Sedaxane Pharmacokinetics in the Rat following a Single Oral Administration of 1 mg or 80 mg [Pyrazole-5-^{14}C]-SYN524464/kg (MRID #47473355).
A mean of 91.6% or 97.2% AD was eliminated in urine and feces over 72 h by male and female rats. The major route of elimination was via the feces; however, urinary elimination was also an important route of excretion in both sexes and slightly more pronounced in females compared to males. Recoveries of radioactivity ranged between 91.5-101.1% AD. Concentrations of [pyrazole-5-^{14}C]-SYN524464 were slightly higher in plasma than in whole blood at most time points, suggesting that total radioactivity was relatively evenly distributed between them. In general, T_{max} was achieved at 1-6 h post dose and declined with estimated terminal half-life values ranging from 22.65-28.76 h. Terminal half-life values of 20.71-39.86 h were obtained for blood. There were no apparent differences in the AUC and C_{max} values between genders, or between the dose levels. As doses of [pyrazole-5-^{14}C]-SYN524464 were increased from 1 to 80 mg/kg bw, systemic exposure to total radioactivity exhibited a 118-140 fold increase but, due to the observed variability in the concentrations for individual rats, this was not considered significant.

Sedaxane Excretion in Bile Duct Cannulated Rats Following Single Oral Administration of 1 mg or 80 mg [Pyrazole-5-^{14}C]-SYN524464/kg (MRID #47473357).
The majority of the administered radioactivity was excreted within the first day post-dose for both dose levels. Absorption was estimated to be 87-89% AD in males and 88-92% AD and females. Fecal excretion and gastrointestinal tract contents were less than 7% AD. Biliary excretion represented the predominant excretion route for both sexes at 79-82% AD. Urinary excretion of the absorbed dose was limited, accounting for approximately 6-7% AD in males and 7-10% AD in females.

Sedaxane Excretion in Bile Duct Cannulated Rats Following Single Oral Administration of 1 mg or 80 mg [Phenyl-U-^{14}C]-SYN524464/kg (MRID #47473360).
There were no significant differences in absorption and elimination patterns between dose levels or between genders.For both dose groups, the majority of the administered radioactivity was excreted within the first day post-dose and biliary excretion represented about 79-85% AD, with urinary excretion, accounting for approximately 5-8% AD. Absorption was estimated to be 87-94% AD (urine radioactivity, cage washes, bile and residual carcass) with fecal excretion and GI tract contents were less than 7% AD.

Sedaxane Tissue Depletion in the Rat Following Single Oral Administration of 1 mg or 80 mg [Pyrazole-5-^{14}C]-SYN524464/kg (MRID #47473358).
The tissue distribution of a single oral dose of 1 or 80 mg [pyrazole-5-^{14}C]-SYN524464/kg bw was extensive. Plasma half-lives ranged from 25.84-32.33 h for both dose group and half-lives in the whole blood ranged from 29.49-40.10 h. Tissue concentrations of radioactivity were highest at 1-1.5 h for low dose and 5 h for high dose with progressively decreased thereafter with elimination half lives of 0.1-3.2 days. Most mean tissue concentrations were near the limit of reliable measurement by 96 h post dose. The high levels of radioactivity in the gastrointestinal tract and its contents were consistent with the established biliary elimination and fecal excretion

of SYN524464 metabolites. There were no pronounced sex differences in tissue distribution, depletion profiles, or half-lives of elimination in the plasma or whole blood.

Sedaxane Investigation of the Nature and Identity of Radiolabelled Metabolites Present in Plasma, Urine, Faeces and Bile Collected from Rats Following Oral Administration of [^{14}C]-SYN524464 (MRID #47473356)
The major metabolites were the *trans* para phenol CSCD658906 and the desmethyl *trans* para phenol CSCD659087 which together with the equivalent *cis* para phenol isomers. Sedaxane was extensively metabolized by rats through demethylation, hydroxylation, oxidation and conjugation pathways resulting in a number of hydroxylated metabolites and metabolites formed by cleavage of the terminal cyclopropyl moiety. Glucuronic acid, sulphate and glutathione conjugates were also formed. CSCD659090 and CSCD668404 accounted for approximately half the administered dose.

Sedaxane Tissue Distribution and Elimination in the Rat Following Repeated Daily Oral Administration of 1 mg [Pyrazole-5-^{14}C]-SYN524464/kg (MRID #47473362).
The majority of the oral administered radioactivity was excreted *via* the feces at 60.9% AD over the 24 h collection period, with urinary excretion at 13.0% AD. Recovery of administered radioactivity was incomplete by 24 h post-dose with a mean of 75.7% AD. Similar results were obtained after 14 daily dosings, with some of the dosing from day 13 also contributing to the day 14 elimination. Tissue concentrations of radioactivity were highest at 24 h following the fourteenth and final dose with the exception of whole blood and plasma, for which the highest mean concentrations were observed 24 h after the tenth dose. The liver and kidney had the highest levels after 14 daily dosings, respectively. Most mean tissue concentrations appeared either to have attained or to be approaching steady state kinetics by the end of the 14 day dosing period. The high levels of radioactivity in the gastrointestinal tract and its contents were consistent with the established biliary elimination and fecal excretion of sedaxane metabolites. There were no pronounced sex differences in tissue distribution, depletion profiles, or half-lives of elimination in the plasma or whole blood.

2. Mutagenicity:

Sedaxane and its metabolite CSCD465008 were negative in all genotoxicity studies, with the results listed below. Sedaxane has been examined in a range of *in vitro* and *in vivo* genotoxicity assays, including endpoints of gene mutation, chromosomal damage and DNA repair. *In vitro*, sedaxane was negative for gene mutation in bacteria (Ames test) and mammalian cells (L5178Y TK$^{+/-}$ mouse lymphoma). The L5178Y TK$^{+/-}$ assay, which is also able to detect chromosomal damage by assessment of colony sizes (small and large colony sizes are associated with clastogenic or mutagenic effects respectively), was also negative for clastogenicity. In the *in vitro* cytogenetic assay using primary human lymphocyte cultures, sedaxane did not induce chromosomal aberrations.

In vivo, sedaxane was found to be non-clastogenic and non-aneugenic in the rat bone marrow

micronucleus assay. Similarly, there was also no evidence for any induction of DNA damage or repair in the rat liver UDS (unscheduled DNA synthesis) assay, with both studies being conducted up to the limit dose of 2000 mg/kg bw.

All of these studies were classified as acceptable/guideline, and fully satisfy the requirement for the 1991 FIFRA Test Guideline 84-2 for mutagenicity data. Based on these considerations, there is no mutagenic concern for the parent molecule or it metabolite CSCD465008. Summaries of the genotoxicity studies are presented below.

Bacterial Reverse Gene Mutation Assay
(*S. typhimurium and E. coli,* MRID#47473381)
The result was negative with and without S9 activation in *S. typhimurium* strains TA 1535, TA 1537, TA 98 and TA 100 and E. coli strains WP2 uvrA pKM 101 and WP2 pKM 101for increased frequency of revertant colonies up to precipitating concentrations (>1000 μg/plate). The positive controls induced an appropriate response.

Mammalian Cell *in vitro* Forward Gene Mutation
(Thymidine Kinase Locus (Tk $^{+/-}$) in Mouse Lymphoma L5178Y Cells, MRID 47473383) The result was negative for increased frequency of mutation when tested up to cytotoxic or precipitating concentrations (>108.8 μg/mL without S9 and >82.5 μg/mL with S9). The positive controls induced the appropriate response.

Mammalian *in vitro* Cytogenetic Assay
(Chromosome Aberration Test in Human Lymphocytes, MRID 47473382)
The result was negative for induction of chromosomal aberrations above background in the presence or absence of S9 metabolic activation up to precipitating concentrations (>216.8 μg/mL). Positive controls induced the appropriate response. In the absence of S9 mix, cytotoxicity was observed at the highest evaluated concentration.

Mammalian *in vivo* Micronucleus Assay
(Mouse Bone Marrow, MRID 47473384)
The result was negative for induction of increased frequency of micro-nucleated polychromatic erythrocytes in bone marrow at any treatment time. There were no signs of toxicity during the study when sedaxane was tested at a limit dose. The positive control induced the appropriate response.

Unscheduled DNA Synthesis (UDS) with Mammalian Liver Cells *In Vivo*
(Rats, MRID 47473385)
The result was negative for inducing unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts] when tested up to a limit dose. Clinical signs of toxicity at 2000 mg/kg bw included hunched posture, lethargy and pilo-erection. The positive controls induced the appropriate response.

Metabolite of Sedaxane: CSCD465008 Genotoxicity Results

The sedaxane metabolite CSCD465008 in plants (not rats) was negative in gentoxicity assay, with the details listed below.

Gene Mutations

(i) In two independent trials of the bacterial reverse gene mutation assay (MRID 47746852), CSCD465008, (94%), was neither cytotoxic nor mutagenic in either the plate incorporation or the preincubation test when assayed up to the limit concentration (5000 *u*g/plate +/-S9) in *S. typhimurium* TA1535, TA1537, TA98 or TA100 or in *E. coli* WP2 (pKM101) or WP2 *uvrA* (pKM101).

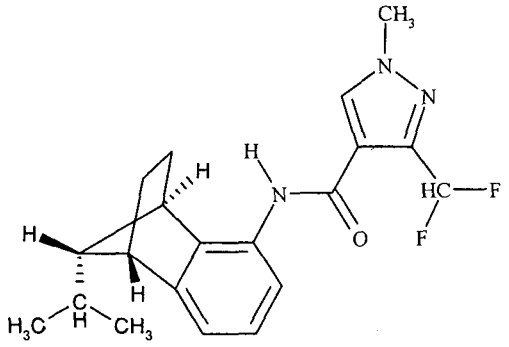
(ii) In an *in vitro* mammalian cell forward gene mutation assay ((MRID 47746856), CSCD465008, (94%) was neither cytotoxic nor mutagenic in L5187Y ($TK^{+/-}$) cells in two independently performed test up to the limit concentration (10mM, equivalent to 1760 *u*g/mL +/– S9).

Chromosome Aberrations

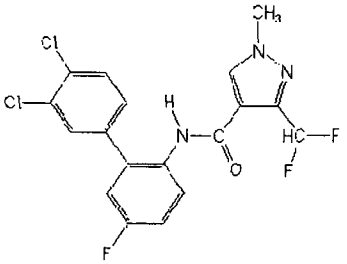
(iii) In an *in vitro* chromosome assay (MRID 47746860), human lymphocytes, derived from the peripheral blood of two female donors were exposed to CSCD465008 (94%) for 4 hours at 574.7, 1005.7 and 1760.0 ug/mL –S9 or 328.4, 574.7 or 1005.7 ug/mL +S9 (Trial 1) or continuously for 22 hours to 574.7, 1005.7 and 1760.0 ug/mL -S9 or for 4 hours to 574.7, 1005.7 and 1760.0 ug/mL +S9 (Trial 2). The highest dose tested (1760.0 ug/mL) represents the limit concentration (10mM) for this test system. Slight but significant ($p<0.05$) increases in the percentage of aberrant cells were seen at 574.7 ug/mL –S9 and at 1760.0 ug/mL +S9 after 4 hours of exposure. However, the responses were within the historical range of the performing laboratory or not replicated. Accordingly, CSCD465008 is not considered to be clastogenic in this *in vitro* human lymphocytes test system.

3. Structure-Activity Relationship

Sedaxane is a member of the pyrazole-carboxamide class of succinate dehydrogenase inhibitor fungicides. Other similar analogs include bixafen and isopyrazam (see structures below). The chemicals are new and the toxicology literature is limited. Isopyrazam and sedaxane produce the same metabolite CSCD465008 in crops, not rats (see below). CSCD465008 is not genotoxic, however it is inconclusive whether it is generally more or less toxic than sedaxane, since the 28-day toxicology study was done in rats for CSCD465008 and the same study for sedaxane in mice. Isopyrazam was classified by the CARC as "Likely to be Carcinogenic to Humans" based on the presence of thyroid follicular cell tumors in male rats, and liver and uterine tumors in female rats (TXR No. 0055619).

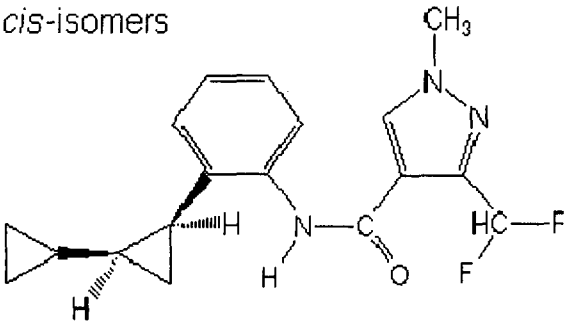


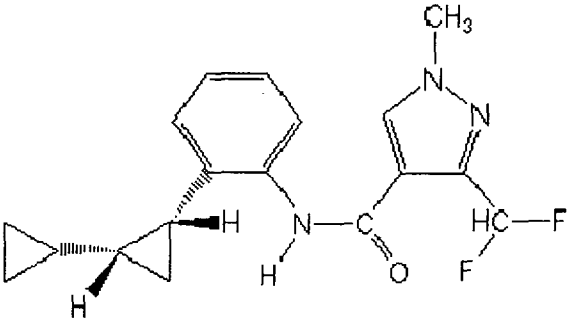
Isopyrazam



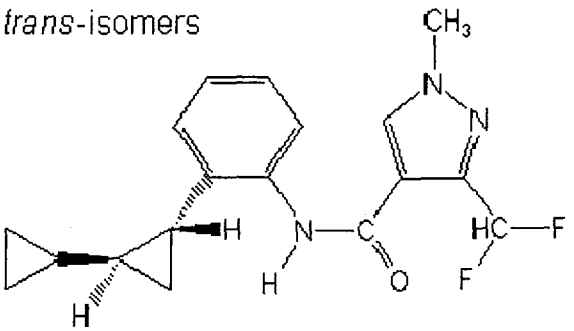
Bixafen

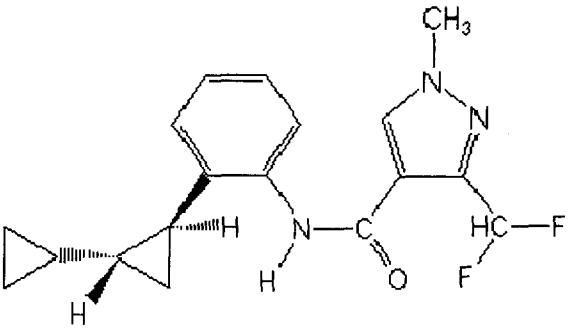
cis-isomers

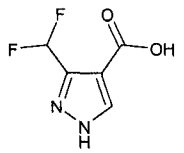




trans-isomers







CSCD465008 Metabolite

4. Sub-chronic and Chronic Toxicity

a) Sub-chronic Toxicity

(1) RAT

28-Day Dietary Toxicity Study in the Wistar Rat

NOAEL=37.8/40.1 mg/kg bw/day M/F
LOAEL=153.5/156.4 mg/kg/day M/F

Sedaxane was administered via the diet at dose levels of 0,500, 2000 or 5000 ppm (equal to 0, 37.8, 153.5, 360.1 mg/kg bw/day in males and 0, 40.1, 156.4, 338.8 mg/kg bw/day in females) for 28 days. The LOAEL is based on food efficiency was decreased in males and females at ≥153.5/156.4 mg/kg bw/day M/F. Reduced food intake and decreased body weight and body weight gains were observed only in females at 156.4 mg/kg bw/day and both sexes at 360.1/338.8 mg/kg bw/day M/F. All rats survived until scheduled termination. There were no treatment-related effects on clinical signs, detailed behavioral observations or gross pathology. There were no organ weights or histology data in this range-finding study.

90-Day Dietary Toxicity Study in Wistar Rats

NOAEL = 24.8/28.3mg/kg/day M/F
LOAEL = 168/186 mg/kg/day M/F

The LOAELs were based on decreased bodyweight (-10%) and body weight gain (-19%) in females and decreased fore grip strength in both sexes (-22-23%). There was a 15% increase in the adjusted liver weight in males at 168 mg/kg/day and a 25% increase in the adjusted liver weight in females at 186 mg/kg/day. There was a 32% decrease in the adjusted thyroid weight in males at 24.8 mg/kg/day and a 10% decrease in the kidney weight in females at 186 mg/kg/day. Longer-term studies revealed liver tumor formation and thyroid tumors in males.

(2) MICE

4-Week CD-1 Mouse Dietary Preliminary Study

NOAEL=1268/1800 mg/kg/day M/F
LOAEL=NA/NA mg/kg/day M/F

CD-1 mice were treated with sedaxane in the diet at dose levels of 0, 1000, 5000 or 7000 ppm for 28 days. There were only changes in clinical chemistry, such as a decrease in mice calcium levels by 16% in males (over 5 SD from the mean), at 1268 mg/kg/day (p=0.01). The triglycerides increased by 64% at 1268 mg/kg/day in males (p=0.05). Both clinical chemistry effects were dose responsive; however, these changes were not accompanied by any micropathology findings.

90-Day CD-1 Mouse Preliminary Carcinogenicity Study

NOAEL=567/1455 mg/kg/day
LOAEL=1167/NA mg/kg/day

The LOAEL is based on a 32% decrease in body weight gains in males at 13 weeks. In femalesat 90 days, the body weight gain decreased 23% at 810 mg/kg/day, but increased 30% at 1455 mg/kg/day; however, both changes were not statistically significant. Also, WBC decreased by 35% in males (p=0.05) at 1167g/kg/day and lymphocytes decreased by 44% in males at 1167 mg/kg/day, both beyond the normal control ranges. In males, the adjusted liver weight increased 11% at 80 mg/kg/day (liver tumor formation was observed in longer studies) and the adjusted testis weight increased 16% at 567 mg/kg/day.

b) Chronic Toxicity

(3) RAT

In a chronic toxicity study, sedaxane (95.3% a.i.) was administered to 52 Crl:WI(Han) (Han Wistar) rats/sex/dose in diet at dose levels of 0, 200, 1200 or 3600 ppm (0, 11, 67 or 218 mg/kg bw/day in males and 0, 14, 86 or 261 mg/kg bw/day in females) for at least 104 consecutive weeks. In addition, a toxicity study comprising 12 Han Wistar rats/sex/dose were included and dosed in an identical fashion for a period of 52 consecutive weeks.

Changes in males less than 10% or within normal ranges were not considered adverse: body weight, BWG, GGT, serum protein, pro-thrombin times, globulin, albumin, and glucose.

In males, the LOAEL of 67 mg/kg/day was based on phosphate increases of 20% and thyroid follicular cell hypertrophy. The phosphate changes could be linked to the kidney pathology and tissue mass increase potentially leading to thyroid adenomas at higher doses.

A decrease in body weight and body weight gain was observed in males at 218 mg/kg bw/day (-18% and -19 to -32%, respectively) and in females at 261 mg/kg bw/day (-33% and -50%, respectively). A corresponding decrease in food consumption and food efficiency was observed in males (-14% and -21%, respectively) and females (-16% and -26%, respectively) at the high-dose.

In males, in the liver there was also hypertrophy while in thyroid there was hyperplasia and hypertrophy detected. In females, the LOAEL at 261 mg/kg/day is based on a 33% decrease in body weight, a 50% decrease in body weight gain, a 16% decrease in food consumption and a 26% decrease in food efficiency. Also in females, a 28% increase in phosphate, increased liver hypertrophy & pigmentation & weight, kidney changes, vaginal mucification decrease and increased thyroid follicular cell hyperplasia. The decreases in AST and ALT were not considered adverse.

In the chronic toxicity study, a dose related statistically significant increase in absolute and adjusted liver weight, (adjusted for body weight by covariate analysis) was seen in mid-dose and high-dose animals. Minimal to moderate centrilobular hepatocyte hypertrophy in the liver was seen in all females at 261 mg/kg bw/day and most males at 218 mg/kg bw/day. Additionally in these groups, there was a statistically significant increase in the incidence of pigment in centrilobular or mid-zonal hepatocytes. Minimal to mild thyroid follicular cell hypertrophy was seen in some animals of both sexes dosed at 67 or 86 mg/kg bw/day and above.

In the carcinogenicity study, a dose related statistically significant increase in adjusted liver weight was seen in mid- and high-dose males and females. The absolute liver weights were also statistically significantly higher than controls for mid- and high-dose males. The incidence of hepatocyte hypertrophy was increased in males dosed with 67 or 218 mg/kg bw/day and females dosed with 261 mg/kg bw/day compared to their respective controls. Increased epithelial tubular hyperplasia of the thymus was observed in high-dose females.

(4) MICE

Sedaxane was administered in diet to groups of CD-1 mice (50/sex/group) at dose levels of 0, 200, 1250 or 7000 ppm (0, 25, 157, and 900 mg SYN524464/kg/day for males and 0, 29, 185, and 1001 mg SYN524464/kg/day for females) for 80 weeks.

Body weight and food consumption changes were less than 10%, so not considered adverse.

The LOAEL of 900/1001 mg/kg/day is based on lower body weight gains (-27% in both genders) and decreased feed efficiency (-19 to -25%).

Increased incidences of hepatocellular adenomas and/or carcinomas were seen in male mice at the high dose compared to concurrent controls. This finding was considered treatment-related, but at a dose level that approached a limit dose (900 mg/kg/day). Sedaxane was not oncogenic in female mice. Liver adenomas and carcinomas in males were dose-responsive and above the rates in concurrent control CD-1 mice.

5. Mode of Action (MOA) Studies

No formal mode of action framework for these tumors was provided by the registrant for consideration by the CARC. MOA work in rats or mice was not pursued by the registrant. However, there is very early work to further examine liver growth changes (liver biochemistry) in a 28-day rat study, which was part of the submission, done with SYN524464 (sedaxane) and its separate isomers. PROD increased (marker of CYP2B induction), marginal increase was seen in EROD (CYP1A marker), no increase in markers of PPAR-alpha activation. No effect on thyroid hormones were reported at 28 days of dietary treatment (MRID 47473372: Peffer, R. and Noakes, J., 2010. Amended - SYN508210, SYN508211 and SYN524464 - 28 Day Comparative Study in the Rat).

V. COMMITTEE'S ASSESSMENT OF THE WEIGHT-OF-THE-EVIDENCE

The Committee considered the following for a weight-of-evidence determination of the carcinogenic potential of Sedaxane:

1. Carcinogenicity

Rat

• *Liver Tumors:* In male Wistar rats, liver tumors were limited to adenomas; no carcinomas were seen. Although a statistically significant trend was seen for liver adenomas at $p<0.05$, there were no significant pair-wise comparisons of the dosed groups with the controls. The concurrent control incidence (2%) was within the laboratory historical control range (0-3%); however, the incidence of liver adenomas at the high dose (10%) exceeded the historical control range. No pre-cursor lesions of the liver were seen in males at this dose. **The CARC considered the liver adenomas to be weak evidence of a treatment-related effect only at the high dose in male rats.**

• *Thyroid Tumors:* Male Wistar rats had statistically significant trends for thyroid follicular cell adenomas and thyroid follicular cell combined adenomas and/or carcinomas, both at $p < 0.05$. There were no significant pair-wise comparisons of the dosed groups with the controls. The concurrent control incidences of adenomas, carcinomas and combined were within the laboratory historical control ranges; however, the combined incidences exceeded the laboratory control ranges. The thyroid tumors were supported by the presence of precursor lesions in the thyroid (increased follicular cell hyperplasia). **The CARC considered the thyroid tumors to be weak evidence of a treatment-related effect only at the high dose in male rats.**

• *Uterine Tumors:* The incidences of combined uterine tumors (adenomas and adenocarcinomas) were significantly increased at all dose levels. No precursor lesions were seen at any dose level. Female Wistar rats had statistically significant trends, and significant pair-wise comparisons of the 3600 ppm dose group with the controls, for uterine adenocarcinomas and combined

adenomas and/or adenocarcinomas, all at $p < 0.01$. There was a statistically significant pair-wise comparison of the 1200 ppm dose group with the controls for uterine combined adenomas and/or adenocarcinomas at $p < 0.05$. There was also a statistically significant pair-wise comparison of the 200 ppm dose group with the controls for uterine adenocarcinomas and combined adenomas and/or adenocarcinomas, both at $p < 0.05$. The CARC observed that uterine tumors were present in structurally related chemicals. **The CARC considered the uterine tumors to be treatment-related in female rats.**

• *Adequacy of Dosing:* In both males and female rats, the high dose of 3600 ppm was considered to be adequate, but not excessive, to assess the carcinogenicity of sedaxane. Significant ($p<0.01$) decreases in absolute body weights were seen in males (17.8%) and females (33.1%). Body weight gains were significantly ($p<0.01$) decreased in males (23.5%) and females (49.1%). Although the observed body weight/body weight gains changes exceeded the conventional 10% criteria employed for assessment of body weight changes in carcinogenicity studies, the CARC did not consider the high dose (3600 ppm) to be excessive in either sex since there was no evidence of adverse toxicity (e.g., mortality, clinical signs at this dose). In addition, significant increases in liver weights were seen in males (absolute and relative) and females (relative), as well as treatment-related non-neoplastic lesions in the liver and thyroid glands in both sexes and in the kidneys and vagina in the females. Survival in males and females was not affected at the high dose.

Mouse

• *Liver Tumors:* Male CD-1 mice had statistically significant trends, and significant pair-wise comparisons of the 7000 ppm dose group with the controls, for hepatocellular adenomas and combined adenomas and/or carcinomas, all at $p < 0.05$. There was also a statistically significant trend in hepatocellular carcinomas at $p < 0.05$. The incidences of liver adenomas, carcinomas and combined exceeded the laboratory historical control ranges. There were no precursor lesions of the liver at this dose. **The CARC considered the liver tumors to be treatment-related only at the high dose in male mice.**

• *Adequacy of Dosing:* The high dose of 7000 ppm was considered to be adequate, but not excessive, in both male and female mice to assess the carcinogenicity of sedaxane. The highest dose tested was the limit dose.

2. Mutagenicity: There is no concern for mutagenicity.

3. Structure Activity Relationship: Sedaxane is a member of the pyrazole-carboxamide class of succinate dehydrogenase inhibitor fungicides. Other similar analogs include bixafen and isopyrazam. Isopyrazam was classified as "Likely to be Carcinogenic to Humans" based on the presence of thyroid follicular cell tumors in male rats, and liver and uterine tumors in female rats.

VI. CLASSIFICATION OF CARCINOGENIC POTENTIAL

In accordance with the EPA's *Final Guidelines for Carcinogen Risk Assessment* (March, 2005), the CARC classified Sedaxane as **"Likely to be Carcinogenic to Humans".** This classification is based on the presence of liver and thyroid tumors in male rats, uterine tumors in female rats and liver tumors in male mice. Uterine tumors were also seen in a chemical structurally related to Sedaxane. There is no mutagenic concern for Sedaxane.

VII. QUANTIFICATION OF CARCINOGENIC POTENTIAL

A linear low-dose extrapolation model (Q_1*) will be used for quantification of cancer risk to humans.

VIII. BIBLIOGRAPHY

MRID No. CITATION

Bibliography of Submitted Toxicology studies for Sedaxane	
47473386	104 Week Rat Dietary Carcinogenicity Study with Combined 52 Week Toxicity Study. Charles River, Tranent, Edinburgh, EH33 2NE, UK. Laboratory Report No. 30196 issue date: 10 February 2010. Unpublished. (Syngenta File No. SYN524464_11306). PMRA #1897899.
47473388	80 Week Mouse Dietary Carcinogenicity Study. Charles River, Tranent, Edinburgh EH33 2NE, UK. Laboratory Report No. 30194 issue date. 28 January 2010. Unpublished. (Syngenta File No. SYN524464_11261). PMRA #1897905.
47473377	90 Day Mouse Preliminary Carcinogenicity Study. Charles River, Tranent, Edinburgh, EH33 2NE, UK. Laboratory Report No. 29170 issue date 17 December 2008. Unpublished. (Syngenta File No. SYN524464_11115). PMRA #1897869.
47473375	90 Day Dietary Toxicity Study in Rats. Syngenta Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, SK10 4TJ, UK. Laboratory Report No. PR1327-REG issue date 23 July 2007. Unpublished. (Syngenta File No. SYN524464/0030). PMRA #1897866.
47473374	4-Week Oral (Capsule) Toxicity Study in the Beagle Dog. Harlan Laboratories Ltd (former RCC Ltd), Zelgliweg 1, 4452 Itingen, Switzerland. Laboratory Report Number B09325. Issue date 09 Dec 2008. Unpublished. (Syngenta File No. SYN524464_11111). PMRA #1897860.
47473379	52-week oral (capsule) toxicity study in the dog. Harlan Laboratories Ltd., Itingen, Switzerland. Laboratory Report Number: B18900, issue date 25 November 2009. Unpublished (Syngenta File No. SYN524464_11223). PMRA #1897881.
47746852	CSCD465008 - Salmonella Typhimurium and Escherichia Coli Reverse Mutation Assay. RCC Cytotest Cell Research GmbH, In den Leppsteinswiesen 19, 64380 Rossdorf Germany. Laboratory Report No. 1129601, issue date. 12 June 2008 Unpublished (Syngenta File No. R958945_10198). PMRA #1897924.
47746860	CSCD465008 - Chromosome Aberration Study in Human Lymphocytes *In Vitro*. RCC Cytotest Cell Research GmbH (RCC-CCR), In den Leppsteinswiesen 19, 64380 Rossdorf, Germany. Laboratory Report No. 1129602, issue date 26 June 2008. Unpublished. Syngenta File No. R958945_10493. PMRA #1897923.
47746856	CSCD465008 - Cell Mutation Assay at the Thymidine Kinase Locus (TK +/-) in Mouse Lymphoma L5178Y Cells. RCC Cytotest Cell Research GmbH, In den Leppsteinswiesen 19, 64380 Rossdorf, Germany. Laboratory Report No. 1129603, 25 April 2008. Unpublished (Syngenta File No.SYN520453_0151). PMRA # 1897922.
47746827	CSCD465008 - A 28-Day Oral (Dietary) Toxicity Study in Wistar Rats. WIL Research Laboratories, LLC, 1407 George Road, Ashland, OH 44805-8946 US. Laboratory Report No. WIL-639008, issue date 19 September 2008. Unpublished. (Syngenta File No R958945_11254). PMRA # 1897920.
47473373	4 Week Mouse Dietary Preliminary Study. Charles River, Tranent, Edinburgh, EN33 2NE, UK. Laboratory Report No. 27927 issue date 16 December 2008. Unpublished. (Syngenta File No. SYN524464_11114). PMRA #1897863.
47473405	A 28-Day Dietary Immunotoxicity Study in CD-1 Male Mice. WIL Research Laboratories, LLC, Ashland, OH. Laboratory Report No. WIL-639053. Issue date: 07 April 2010. Unpublished. (Syngenta File No. SYN524464_11333). PMRA #

Bibliography of Submitted Toxicology studies for Sedaxane	
	1897837.
47473372	SYN508210, SYN508211 and SYN524464 - 28 Day Comparative Study in the Rat. Syngenta Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire, SK10 4TJ, UK. Laboratory report No. KR1595-TEC-Amendment 1. Issue date10 July 2007. Amendment 1 issued 26 February 2010. Unpublished. (Syngenta File No. SYN508210/0005). PMRA #1897840.
47473396	Acute Oral (Gavage) Neurotoxicity Study in Rats. Harlan Laboratories Ltd. (formerly RCC Ltd), Zelgliweg 1, CH-4452 Itingen / Switzerland. Laboratory Report No. B86591. Issue Date 08 October 2009. Unpublished (Syngenta File No.SYN524464_11145). PMRA #1897914.
47473398	90 Day Neurotoxicity (Dietary) Study in the Rat. Harlan Laboratories Ltd., (formerly RCC Ltd), Zelgliweg 1, CH-4452 Itingen / Switzerland. Laboratory Report No. B67432. Issue date 29 Oct 2009. Unpublished. (Syngenta File No. SYN524464_11148). PMRA #1897918.
47473397	28-Day Dietary Toxicity Study in the Rat (Preliminary to a 90-Day Neurotoxicity Study).
TXR No. 0055689	Brunsman, L., 2011. Sedaxane Qualitative Risk Assessment Based on Crl:WI(Han)(Han Wistar) Rat and Crl:CD-1(ICR) Mouse Dietary Studies. 2/23/11. TXR No. 0055689
TXR No. 0055845	Brunsman, L., 2011. Sedaxane Quantitative Risk Assessment Based on Crl:WI(Han)(Han Wistar) Rat and Crl:CD-1(ICR) Mouse Dietary Studies. 4/26/11. TXR No. 0055845

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